

Application No. 10/609,120
 Atty Dkt No. 11187-00016 (Endow-3-US)
 Reply to Office Action of October 3, 2006

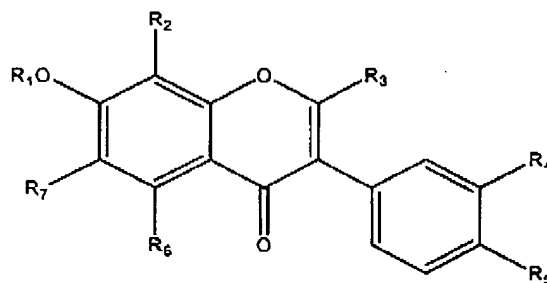
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APPENDIX A

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7. A method of reducing alcohol consumption in a mammal comprising administering a compound of Formula I



Formula I

wherein:

R₁ is selected from the group consisting of hydrogen, carboxy, halo, branched or straight chain (C₁-C₆)haloalkyl, (C₃-C₆)cycloalkoxy, (C₁-C₆)haloalkoxy, (C₃-C₆)cyclohaloalkoxy, (C₃-C₆)cycloalkoxyalkyl, (C₁-C₆)alkoxy(C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkylcarbonyl, substituted or unsubstituted phenyl, phenyl(C₁-C₆)alkyl, and heterocyclyloxy, heterocyclylcarbonyl, wherein substituents are from one to four and are selected from the group consisting of halo, aminocarbonyl, aminothiocarbonyl, carboxy, formyl, hydroxy, amino, carbamoyl, (C₁-C₃)alkyl, (C₁-C₃)haloalkyl, (C₁-C₃)alkoxy, (C₁-C₃)haloalkoxy, (C₁-C₃)alkylamino, di(C₁-C₃)alkylamino, (C₁-C₂)alkoxy(C₁-C₂)alkyl, (C₁-C₂)alkylamino(C₁-C₂)alkyl, di(C₁-C₂)alkylamino(C₁-C₂)alkyl, (C₁-C₃)alkylcarbonyl, (C₁-C₃)alkoxycarbonyl, (C₁-C₃)alkylaminocarbonyl, and di (C₁-C₃)alkylaminocarbonyl;

R₂ is selected from the group consisting of hydrogen and alkoxy;

R₃ is selected from the group consisting of hydrogen, (C₁-C₆) alkoxycarbonyl, and carboxy;

R₄ is selected from the group consisting of hydrogen and hydroxy;

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R₅ is selected from the group consisting of hydrogen, carboxy, hydroxy, amino, halo, branched or straight chain (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₃-C₆)alkadienyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₁-C₆)haloalkoxy, (C₃-C₆)cyclohaloalkoxy, (C₂-C₆)alkynyloxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkoxyalkyl, (C₁-C₆)alkoxy(C₃-C₆)cycloalkyl, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₁-C₆)alkoxycarbonyl, (C₄-C₆)alkoxycarbonylalkyl, (C₁-C₆)hydroxyalkyl, substituted or unsubstituted phenyl, phenyl(C₁-C₆)alkyl, heterocyclyl, heterocycliloxy, heterocyclylcarbonyl, wherein substituents are from one to four and are selected from the group consisting of halo, aminocarbonyl, aminothiocarbonyl, carboxy, formyl, hydroxy, amino, carbamoyl, (C₁-C₃)alkyl, (C₁-C₃)haloalkyl, (C₁-C₃)alkoxy, (C₁-C₃)haloalkoxy, (C₁-C₃)alkylamino, di(C₁-C₃)alkylamino, (C₁-C₂)alkoxy(C₁-C₂)alkyl, (C₁-C₂)alkylamino(C₁-C₂)alkyl, di(C₁-C₂)alkylamino(C₁-C₂)alkyl, (C₁-C₃)alkylcarbonyl, (C₁-C₃)alkoxycarbonyl, (C₁-C₃)alkylaminocarbonyl, and di (C₁-C₃)alkylaminocarbonyl;

R₆ is selected from the group consisting of hydrogen and hydroxy; and

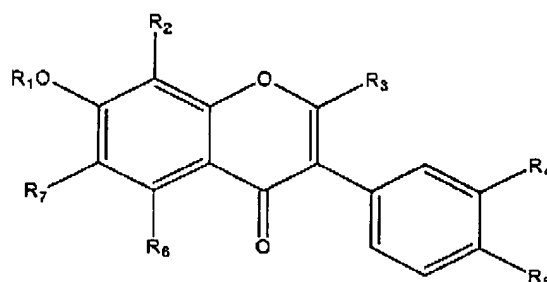
R₇ is selected from the group consisting of hydrogen and halogen,

with the proviso that R₅ cannot be hydroxy when R₁, R₂, R₃, R₄, R₆, and R₇ are all hydrogen

in an amount effective to increase a concentration of 5-hydroxyindoleacetaldehyde formed during catabolism of serotonin or dopamine.

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8. A method of modulating alcohol consumption in a mammal comprising administering a compound of Formula I



Formula I

wherein:

R₁ is selected from the group consisting of hydrogen, carboxy, halo, branched or straight chain (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₃-C₆)alkadienyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₁-C₆)haloalkoxy, (C₃-C₆)cyclohaloalkoxy, (C₂-C₆)alkynyloxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkoxyalkyl, (C₁-C₆)alkoxy(C₃-C₆)cycloalkyl, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₁-C₆)alkoxycarbonyl, (C₄-C₆)alkoxycarbonylalkyl, (C₁-C₆)hydroxyalkyl, (C₅-C₁₀)carboxyalkyl, substituted or unsubstituted phenyl, phenyl(C₁-C₆)alkyl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, wherein substituents are from one to four and are selected from the group consisting of halo, aminocarbonyl, aminothiocarbonyl, carboxy, formyl, hydroxy, amino, carbamoyl, (C₁-C₃)alkyl, (C₁-C₃)haloalkyl, (C₁-C₃)alkoxy, (C₁-C₃)haloalkoxy, (C₁-C₃)alkylamino, di(C₁-C₃)alkylamino, (C₁-C₂)alkoxy(C₁-C₂)alkyl, (C₁-C₂)alkylamino(C₁-C₂)alkyl, di(C₁-C₂)alkylamino(C₁-C₂)alkyl, (C₁-C₃)alkylcarbonyl, (C₁-C₃)alkoxycarbonyl, (C₁-C₃)alkylaminocarbonyl, and di (C₁-C₃)alkylaminocarbonyl;

R₂ is selected from the group consisting of hydrogen and alkoxy;

R₃ is selected from the group consisting of hydrogen, (C₁-C₆) alkoxycarbonyl, and carboxy;

R₄ is selected from the group consisting of hydrogen and hydroxy;

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R₅ is selected from the group consisting of hydrogen, carboxy, halo, amino, branched or straight chain (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₃-C₆)alkadienyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₁-C₆)haloalkoxy, (C₃-C₆)cyclohaloalkoxy, (C₂-C₆)alkynyloxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkoxyalkyl, (C₁-C₆)alkoxy(C₃-C₆)cycloalkyl, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₁-C₆)alkoxycarbonyl, (C₄-C₆)alkoxycarbonylalkyl, (C₁-C₆)hydroxyalkyl, substituted or unsubstituted phenyl, phenyl(C₁-C₆)alkyl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, wherein substituents are from one to four and are selected from the group consisting of halo, aminocarbonyl, aminothiocarbonyl, carboxy, formyl, hydroxy, amino, carbamoyl, (C₁-C₃)alkyl, (C₁-C₃)haloalkyl, (C₁-C₃)alkoxy, (C₁-C₃)haloalkoxy, (C₁-C₃)alkylamino, di(C₁-C₃)alkylamino, (C₁-C₂)alkoxy(C₁-C₂)alkyl, (C₁-C₂)alkylamino(C₁-C₂)alkyl, di(C₁-C₂)alkylamino(C₁-C₂)alkyl, (C₁-C₃)alkylcarbonyl, (C₁-C₃)alkoxycarbonyl, (C₁-C₃)alkylaminocarbonyl, and di (C₁-C₃)alkylaminocarbonyl;

R₆ is selected from the group consisting of hydrogen and hydroxy; and

R₇ is selected from the group consisting of hydrogen, halogen, and C₁-C₆ alkoxy,

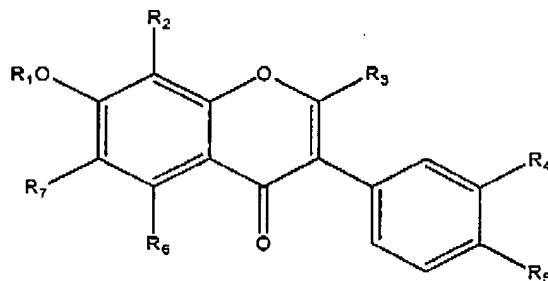
in an amount effective to increase a concentration of 5-hydroxyindoleacetaldehyde or 3,4-dihydroxyphenylacetaldehyde formed during catabolism of serotonin or dopamine.

9. The method of claim 7, wherein the mammal is a human.
12. The method of claim 7, wherein the compound does not inhibit monoamine oxidase.
13. The method of claim 7, wherein R₅ is hydroxyl or amino.
14. The method of claim 8, wherein R₁ is a straight chain alkyl.
15. The method of claim 8, wherein R₁ is (C₁C₆)hydroxyalkyl or (C₅C₁₀)carboxyalkyl.

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16. The method of claim 7, wherein the compound is administered intraperitoneally, intramuscularly or orally.

27. A compound for inhibiting ALDH-2 comprising Formula I



Formula I

wherein:

R₁ is selected from the group consisting of hydrogen, carboxy, halo, amino, branched or straight chain (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₃-C₆)alkadienyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₁-C₆)haloalkoxy, (C₃-C₆)cyclohaloalkoxy, (C₂-C₆)alkynyloxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkoxyalkyl, (C₁-C₆)alkoxy(C₃-C₆)cycloalkyl, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₁-C₆)alkoxycarbonyl, (C₄-C₆)alkoxycarbonylalkyl, (C₁-C₆)hydroxyalkyl, (C₅-C₁₀)carboxyalkyl, substituted or unsubstituted phenyl, phenyl(C₁-C₆)alkyl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, wherein substituents are from one to four and are selected from the group consisting of halo, aminocarbonyl, aminothiocarbonyl, carboxy, formyl, hydroxy, amino, carbamoyl, (C₁-C₃)alkyl, (C₁-C₃)haloalkyl, (C₁-C₃)alkoxy, (C₁-C₃)haloalkoxy, (C₁-C₃)alkylamino, di(C₁-C₃)alkylamino, (C₁-C₂)alkoxy(C₁-C₂)alkyl, (C₁-C₂)alkylamino(C₁-C₂)alkyl, di(C₁-C₂)alkylamino(C₁-C₂)alkyl, (C₁-C₃)alkylcarbonyl, (C₁-C₃)alkoxycarbonyl, (C₁-C₃)alkylaminocarbonyl, and di (C₁-C₃)alkylaminocarbonyl;

R₂ is selected from the group consisting of hydrogen and alkoxy;

R₃ is hydrogen;

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R₄ is selected from the group consisting of hydrogen and hydroxy;

R₅ is selected from the group consisting of hydrogen, carboxy, halo, amino, branched or straight chain (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₃-C₆)alkadienyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₁-C₆)haloalkoxy, (C₃-C₆)cyclohaloalkoxy, (C₂-C₆)alkynyloxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkoxyalkyl, (C₁-C₆)alkoxy(C₃-C₆)cycloalkyl, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₁-C₆)alkoxycarbonyl, (C₄-C₆)alkoxycarbonylalkyl, (C₁-C₆)hydroxyalkyl, substituted or unsubstituted phenyl, phenyl(C₁-C₆)alkyl, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, wherein substituents are from one to four and are selected from the group consisting of halo, aminocarbonyl, aminothiocarbonyl, carboxy, formyl, hydroxy, amino, carbamoyl, (C₁-C₃)alkyl, (C₁-C₃)haloalkyl, (C₁-C₃)alkoxy, (C₁-C₃)haloalkoxy, (C₁-C₃)alkylamino, di(C₁-C₃)alkylamino, (C₁-C₂)alkoxy(C₁-C₂)alkyl, (C₁-C₂)alkylamino(C₁-C₂)alkyl, di(C₁-C₂)alkylamino(C₁-C₂)alkyl, (C₁-C₃)alkylcarbonyl, (C₁-C₃)alkoxycarbonyl, (C₁-C₃)alkylaminocarbonyl, and di (C₁-C₃)alkylaminocarbonyl.

R₆ is selected from the group consisting of hydrogen and hydroxy; and

R₇ is selected from the group consisting of hydrogen, halogen, and C₁-C₆ alkoxy.

28. The compound of claim 26, wherein R₅ is hydroxyl or amino.
29. The compound of claim 27, wherein R₁ is a straight chain alkyl.
30. The compound of claim 27, wherein R₁ is (C₁-C₆)hydroxyalkyl or (C₅-C₁₀)carboxyalkyl.

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